Texarkana —
Epidemic Measles in a Divided City

Instructor's Guide

Learning Objectives
After completing this case study, the participant should be able to:

☐ Discuss the advantages and disadvantages of using a sensitive and/or specific case definition in an epidemic investigation;

☐ Calculate vaccine efficacy and discuss its interpretation; and

☐ Discuss the advantages and limitations of selecting a specific age as the recommended target date for administering vaccinations.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

CDC
CENTERS FOR DISEASE CONTROL
AND PREVENTION

PART I

On Tuesday, November 3, 1970, the Center for Disease Control (CDC) in Atlanta received the weekly telegram of surveillance data from the Texas State Health Department. The telegram reported 319 cases of measles in the state during the previous week. In contrast, Texas had reported an average of 26 cases per week during the previous four weeks. In follow-up telephone calls, CDC learned from State health officials that 295 cases of measles had been diagnosed in the city of Texarkana, including 25 in children reported to have been previously immunized.

An invitation to investigate the situation was extended to the CDC on November 4, 1970. An EIS officer departed for Texarkana early on November 5.

Background

Texarkana is a city of roughly 50,000 that straddles the Texas-Arkansas state line.

Texarkana, Texas (Bowie County), had a population of 29,393 in the 1960 census; the population had been stable during the 1960s. Texarkana, Arkansas (Miller County), had a 1960 population of 21,088.

Although Texarkana is divided by the state line, it is a single town economically and socially. Persons of all ages on both sides of town have frequent contact. Churches, physicians, offices, movie theatres, and stores draw people from both the Arkansas and Texas sides of town. People cross the state line to attend social functions such as football games and school dances. Many families have friends and relatives who visit back and forth on both sides of town. Private nurseries and kindergartens receive children from both sides of town. The two sides of Texarkana, however, do have separate public school systems and separate public health departments.

Question 1:   List the reasons to investigate a suspected outbreak. Which reasons may have prompted an investigation of this outbreak?

Answer 1
In general, there are several reasons for undertaking an outbreak investigation. Considerations include:
1. Opportunity or need to control the outbreak;
2. Opportunity to gain further knowledge, e.g., of the agent, cause, or mode of transmission;
3. Training;
4. Public concern, political pressure and/or legal considerations;
5. Programmatic considerations, e.g., to evaluate diagnostic, prevention, or control measures.

These factors, in turn, are often influenced by:
•   Magnitude of the outbreak (depends on disease, however; a few cases of an unusual disease may merit investigation);
•   Serious illness (high morbidity or mortality);
•   Strange or unknown disease.

This investigation was probably done for reasons #1 (need to control), and #5 (evaluate vaccine efficacy), influenced by the size of the outbreak.

Question 2a: What would be the initial steps of your investigation, i.e., the steps before trying to find additional cases?

Answer 2a
1. Administrative steps - prepare for field work, agree on roles, arrange to meet the appropriate authorities, etc.
2. Confirm the existence of an epidemic.
3. Confirm the diagnosis: see and talk with a couple of cases, if possible.
4. Develop a working case definition.

Question 2b: How might you look for additional cases?

Answer 2b
Strategies could include:
•   surveillance data from the two Health Departments (Texas & Arkansas)
•   (in-patient) hospital data
•   (out-patient) physician / clinic records
•   school / day-care records

Question 2c: Once you collected information about the cases, how would you characterize the outbreak?

Answer 2c
Characterize the outbreak by time, place and person (= "perform descriptive epidemiology"):
•   Time – Draw the epidemic curve,
•   Place – Determine the geographic location of the cases and if possible compute measles attack rates by health districts,
•   Person – Determine the main characteristics of the cases: age, sex, vaccine status, link with other cases, source of reporting and if possible compute measles attack rates by age group and vaccination status.

PART II

The Investigation

The investigators obtained names of cases from the health departments, physicians, school and nursery records. They conducted a door-to-door survey. They also asked families of cases for names of other cases. They used the same methods of case-finding and epidemiologic investigation on both the Arkansas and Texas sides of town.

Clinical Picture

The illness was clinically compatible with measles. Typically, the patients had a 4- to 5-day prodrome with high fever, coryza (runny nose), cough, and conjunctivitis (red, irritated eyes) followed by the appearance of a bright maculopapular (red spots and areas) rash. The temperature usually returned to normal 2 to 3 days after appearance of the rash, while the rash persisted for 5 to 7 days.

Question 3:   How might you define a case for purposes of this investigation?

Answer 3
INSTRUCTOR'S NOTE: Review the basic components of a case definition:
   1. clinical features (with or without laboratory findings)
   2. time
   3. place
   4. person

Most communicable diseases have standard epidemiologic case definitions. The standard clinical case definition for measles in use at the time (and similar to the definition in use in 2003) was:
        1. generalized rash lasting three or more days,
   and 2. fever (temperature greater than or equal to 101.0^o F. or 38.3^o C., if measured),
   and 3. one or more of the following - cough, coryza, or conjunctivitis.

For this particular outbreak, the relevant time, place, and person should be specified, e.g.,
   time - since early October (?)
   place - Texarkana, Texas and Arkansas (city only? surrounding areas?)
   person - residents? visitors?

Whatever case definition is used, it must be workable in the context of the outbreak and should take into account how cases are to be identified. Although it may be desirable from the point of view of specificity to define what temperature will constitute fever or to specify maculopapular rash, it may not be a workable definition if the cases are identified by a door-to-door survey -- the family may not have measured the temperature, nor may they be able to provide a sufficiently detailed description of the rash.

In measles outbreaks, cases may be further categorized as either confirmed or probable.

A **confirmed** case is one that is laboratory confirmed (whether it meets the clinical case definition or not), or one that meets the clinical case definition and is epidemiologically linked to a confirmed case.

A **probable** case is one that meets the clinical case definition, but is not linked epidemiologically to another case and has no confirmatory laboratory data.

A laboratory diagnosis consists of either:
   1. Positive serologic test for measles immunoglobulin M antibody,
 or 2. Significant rise in measles antibody level by any standard serologic assay,
 or 3. Isolation of measles virus from a clinical specimen.

Question 4:   Describe the difference between a sensitive case definition and a specific case definition. What are the advantages and disadvantages of each? Provide an example of a situation where each would be helpful.

Answer 4
A sensitive case definition is one with broad or loose criteria, so that it includes, for example, cases with mild symptoms and those without lab confirmation. An even more sensitive case definition than the one used here might be, for example, any rash illness regardless of additional symptoms. The advantage to having a sensitive case definition is that you are likely to include most of the true cases, even those with mild or atypical symptoms. The disadvantage of a sensitive case definition is that it may include persons with a similar illness but not the illness under study. Since with measles there usually are very few atypical cases, using a highly sensitive (and thus less specific) case definition will probably add little to your case ascertainment efficiency. Furthermore, a very sensitive case definition may include some persons with non-measles rashes in the case group which would make it more difficult to identify associations between exposure and illness.

In contrast, a specific case definition is one with strict criteria, usually including laboratory confirmation. A specific case definition tends to exclude non-cases from the case group, but it may also exclude true cases with mild or atypical symptoms and those without lab confirmation. The extra time required to obtain laboratory confirmation may result in unnecessary delay in instituting appropriate control measures. On the other hand, a highly specific case definition is preferred in analytic epidemiology, because it reduces misclassification of the outcome.

Finally, the overall prevalence of a disease and the availability of control measures may influence your choice of a sensitive versus a specific case definition. When the disease is common and few atypical cases occur, a clinical case definition might be appropriate; as a disease becomes less prevalent, as measles has now become, a laboratory-based definition might become increasingly necessary.

In Texarkana, the investigators defined a case as an "illness which is clinically compatible with measles."

**Question 5:**   Critique this case definition.

Answer 5
This case definition would not be acceptable now, because it is vague on at least two counts. First, "clinically compatible" according to whom – the primary care provider? the CDC investigator? other? At the very least, the case definition could have been "physician diagnosis of measles," which was a common formulation of a case definition at the time. Second, even "physician diagnosis" is no longer acceptable, since physician diagnosis varies with the physician's training, knowledge, familiarity with the disease, etc. Today, clinical case definitions are expected to be based on objective criteria such as fever at or above a certain temperature, cough lasting at least a certain number of days, etc.

The Outbreak

Between June 1970 and January 1971, 633 cases of measles were reported from Texarkana. Dates of onset were accurately determined for 535 cases. The epidemic curve is shown below.

Measles cases by week of onset, Texarkana, Texas and Arkansas, June 28, 1970 - January 29, 1971
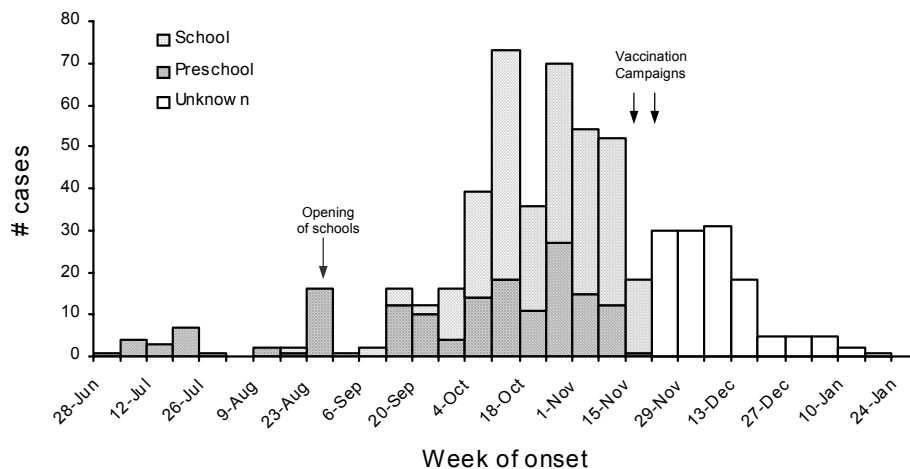
Question 6: Discuss the key features of the epidemic that you can derive from the epidemic curve.

Answer 6
Without data from the period before June 1970, the onset of the epidemic cannot be discerned. The number of cases among preschoolers accelerates sometime in August and for school children in mid-September. The epidemic seems to stop by mid-December, i.e., 2 to 3 weeks (or 1 or 2 incubation periods) after the vaccination campaign. (Vaccine should be effective within 2 weeks.) The shape of the curve suggests that secondary transmission has played an important role in the spread of the epidemic. Because most of the cases are in school-children at the peak of the epidemic, it can be hypothesized that transmission in school has been important. Because the first vaccination session took place at a time when the epidemic was already declining, it is hard to estimate the exact effect of this control measure on the last part of the epidemic curve. Unfortunately, no information is available on the cases that occurred after the vaccination sessions took place: Are they preschoolers? School children?

Though infants, adolescents, and adults were involved in the epidemic, the majority of cases occurred in children 1 to 9 years of age. Measles cases were not evenly distributed within the two counties. Table 1 displays the number of measles cases and population by age group for Bowie County, Texas and in Miller County, Arkansas.

Table 1. Number of measles cases and population (1960 census) by age group and county, Texarkana outbreak, 1970

Residence	Urban/ Rural	Age Group	# Cases	Population	Rate
Bowie Co., Texas	Rural	1-4 yr	47	2,452	____
		5-9	178	3,242	____
		1-9	____	____	____
	Urban	1-4	195	2,481	____
		5-9	73	3,010	____
		1-9	____	____	____
	Total	1-4	242	4,933	____
		5-9	251	6,252	____
		1-9	____	____	____
Miller Co., Arkansas	Total	1-4	19	2,671	____
		5-9	6	3,345	____
		1-9	____	____	____

Question 7: Calculate the totals and attack rates indicated in Table 1.

Answer 7

Residence	Urban/ Rural	Age Group	# Cases	Population	Rate (per 1000)
Bowie Co., Texas	Rural	1-4 yr	47	2452	19.2
		5-9	178	3242	54.9
		1-9	225	5,694	39.5
	Urban	1-4	195	2481	78.6
		5-9	73	3010	24.3
		1-9	268	5,491	48.8
	Total	1-4	242	4933	49.1
		5-9	251	6252	40.1
		1-9	493	11,185	44.1
Miller Co., Arkansas	Total	1-4	19	2671	7.1
		5-9	6	3345	1.8
		1-9	25	6,016	4.2

Question 8: Discuss the differences in attack rates for the Texas and Arkansas counties, for rural versus urban children, and for preschool versus school-age children.

Answer 8

Arkansas vs. Texas: Arkansas has much lower rates than Texas. These differences could be real or artifactual.

Reasons for ARTIFACTUAL differences include:
• different case definitions;
• different surveillance methods;
• wrong denominator data.

Possible explanations for REAL differences in the observed rates include:
• differences in host susceptibility between Texans and Arkansans, resulting from differences in, say, nutritional status, or in socioeconomic status (for measles, more likely to affect severity of illness rather than incidence)
• differences in vaccination policies (including use of different vaccines, e.g., more effective versus less effective vaccine types) and programs (better coverage in Arkansas);
• differences in vaccine handling or administration (e.g., problem with cold chain or cold storage in Texas);
• a prior epidemic in Arkansas that has reduced the number of susceptibles.

Obviously, program differences is the correct explanation for this outbreak.

Rural versus urban: Overall, the attack rate is higher in urban versus rural. This might be expected, since close contact or crowding is more likely to occur in the former situation. Additional information can be obtained, however, by looking at the distribution of attack rates by age.

Preschoolers (1-4 years) versus school age (5-9 years): Overall, the attack rates are higher in preschool children than in school age children. However, the pattern varies by urban/rural residence. In the rural areas, the attack rate is low in the pre-school age group and high in the school age group. In the urban areas the attack rate is high in the pre-school age group and low for the school age group.

The explanation for this observation is that the disease is transmitted among susceptible children when they are grouped together for the first time. In urban areas preschoolers are more likely to be exposed in places such as day-care centers or more crowded home or street environments that those of a comparable age in a rural environment. In the developing world, it is also fairly common to see urban epidemics of measles; in this situation, contact between ill and well children usually occurs in the marketplace or while in contact with the health care delivery system.

Part III

Measles in Previously Vaccinated Children

Before this outbreak, the proportion of children vaccinated against measles on the Arkansas side was substantially higher than the proportion vaccinated on the Texas side. The Texas side had never had a community or school vaccination campaign for measles. In contrast, the Arkansas side had held mass community programs against measles for school and pre-school children in 1968 and 1969.

Based on health department and physician records, investigators estimated that over 99% of children aged 1-9 years in Miller County, Arkansas had received measles vaccine prior to the outbreak. The overall vaccination level in Bowie County, Texas, was estimated to be 57%.

In this outbreak, 27 of the measles cases in Bowie County and all 25 of the measles cases in Miller County gave a history of prior vaccination with live attenuated measles-virus vaccine. Parental history of vaccination was corroborated for all the cases by clinic or physician records. Local health authorities in both counties were very concerned that children who had previously received measles vaccine got the disease.

Question 9: Calculate attack rates among the vaccinated populations in both counties and comment on your findings.

Answer 9

> In Bowie County, Texas:
> > Vaccine coverage = 57%
> > Population 1-9 Years = 11,185
> > Estimated vaccinated population = 11,185 * 0.57 = 6,375
> > Measles cases in previously vaccinated children = 27
> > Attack rate among the vaccinated = 27 / 6,375 = 4.2 per 1,000
>
> In Miller County, Arkansas:
> > Vaccine coverage = 99%
> > Population 1-9 Years = 6,016
> > Estimated vaccinated population = 6,016 * 0.99 = 5,956
> > Measles cases in previously vaccinated children = 25
> > Attack rate among the vaccinated = 25 / 5,956 = 4.2 per 1,000

The attack rate among the vaccinated may be considered the vaccine failure rate. The attack rates (or vaccine failure rates) look similar in the two populations. We need now to look at what happened in the unvaccinated population of Bowie County.

INSTRUCTORS NOTE: You may wish to discuss the relationship between vaccine coverage and the proportion of cases occurring among vaccinated individuals. The fact that all of the cases in Miller County, Arkansas, occurred among vaccinated individuals is to be expected given the extremely high vaccine coverage in the county. For a given level of vaccine efficacy, as the proportion of the population that has been vaccinated increases, an increasing proportion of the cases will have a history of prior vaccination.

Table 2. Hypothetical populations with vaccine coverage of 0%, 20%, 60%, and 100%

	Population			
	A	B	C	D
a. Number of persons in population	100	100	100	100
b. Vaccine efficacy (VE)	90%	90%	90%	90%
c. Percent population vaccinated (PPV)	0%	20%	60%	100%
d. Number vaccinated (a × c)	_____	20	_____	_____
e. Number unvaccinated (a ! d)	_____	80	_____	_____
f. Number protected (d × b)	_____	18	_____	_____
g. Number vaccinated but ill (d ! f)	_____	2	_____	_____
h. Total number ill (e + g)	_____	82	_____	_____
i. Percent cases vaccinated (PCV) (g / h)	_____	2.4%	_____	_____

Consider the use of a vaccine with 90% efficacy in four different hypothetical populations of 100 people each, with vaccine coverage of 0%, 20%, 60%, and 100%, respectively. Assume that every unvaccinated person will be exposed to, and will develop, measles.

Question 10:   Complete Table 2.

Answer 10

	A	B	C	D
a. Number of persons in population	100	100	100	100
b. Vaccine efficacy (VE)	90%	90%	90%	90%
c. Percent population vaccinated (PPV)	0%	20%	60%	100%
d. Number vaccinated (a × c)	0	20	60	100
e. Number unvaccinated (a ! d)	100	80	40	0
f. Number protected (d × b)	0	18	54	90
g. Number vaccinated but ill (d ! f)	0	2	6	10
h. Total number ill (e + g)	100	82	46	10
i. Percent cases vaccinated (PCV) (g / h)	0%	2.4%	13%	100%

Question 11:   What do you conclude about the relationship between coverage and number of cases vaccinated? What might your public health message be for these data?

Answer 11
Seemingly paradoxical result that higher coverage results in higher PCV! In fact, if 100% children were immunized (PPV = 100%), all cases would be in vaccinated children (PCV = 100%). The key public health point, however, is that there would be far fewer total cases of measles.

Vaccine Efficacy

The ability of a vaccine to prevent disease depends on its potency and proper administration to an individual capable of responding. The success of vaccination performed under field conditions may be assessed by measuring protection against clinical disease. Such field assessments can be very useful, particularly when doubt is cast on the efficacy of the vaccine because of the occurrence of disease among vaccinated persons.

Vaccine efficacy is measured by calculating the incidence (attack rates) of disease among vaccinated and unvaccinated persons and determining the percentage reduction in incidence of disease among vaccinated persons relative to unvaccinated persons. The greater the percentage reduction of illness in the vaccinated group, the greater the vaccine efficacy. The basic formula is written as:

$$VE = \frac{ARU - ARV}{ARU} \times 100$$

where
VE   = vaccine efficacy,
ARU = attack rate in the unvaccinated population; and
ARV = attack rate in the vaccinated population.

Question 12:   Using the basic formula, calculate vaccine efficacy for Bowie County, Texas.

Answer 12
The proportion of vaccinated persons who developed measles should be calculated and compared to the proportion of unvaccinated persons who developed measles.

   Attack rate in the vaccinated population (ARV) = 4.2 per 1,000

   Unvaccinated population 1-9 Years = 11,185 - 6,375 = 4,810

   Measles cases in unvaccinated children = 493 - 27 = 466

   Attack rate in unvaccinated population (ARU) = 466 / 4,810 = 96.9 per 1,000

Therefore, vaccine efficacy (VE) is estimated as:

          (96.9 - 4.2) x 100 = 95.7%
              96.9

Measles vaccine is usually estimated to be 95 to 98% effective in developed countries. In developing countries, where immunization is often given before 15 months of age to prevent the high morbidity and mortality occurring in the 9-15 month age group, vaccine efficacy will be lower.

Teaching note: Point out that vaccine efficacy can be algebraically expressed as 1 - RR (x 100). In a case-control study, since OR approximates RR, VE = 1 - OR (x 100).

Four major factors can affect vaccine efficacy calculations:
          1. case definition,
          2. case reporting,
          3. exposure rates in vaccinated and unvaccinated, and
          4. vaccination status determination.
If ARU is falsely elevated or if ARV is falsely decreased, then VE will be falsely increased. If ARV is falsely elevated or if ARU is falsely decreased, then VE will be falsely decreased.

Question 13: Was inadequate vaccine efficacy primarily responsible for this outbreak? If not, what is your alternative explanation?

Answer 13
No, vaccine efficacy was in an acceptable range. The outbreak probably occurred as a result of inadequate vaccine coverage in Texas.

Question 14: What are the possible causes for the failure of the vaccine to protect vaccinated children from acquiring disease?

Answer 14
- Problem with vaccine itself (lack of potency), e.g., defect in the production process
- Problem with vaccine storage and handling, e.g., defect in the cold chain
- Problem with vaccine administration, e.g., improper route or site of vaccination
- Host factors, i.e., inability of the recipient to respond to the vaccine stimulation, e.g., vaccination too young (in presence of maternal antibodies), underlying pathology or concurrent injection (In 1970, immunoglobulins were usually given with measles vaccine to reduce vaccine reactions)
- Change in agent (never reported before for measles)

Part IV

In previously vaccinated children aged 1-9 years in Bowie County, the measles attack rate in this outbreak was 4.2 per 1000; the comparable rate in unvaccinated children was 96.9 per 1000. From these data, a vaccine efficacy of 95.7 percent was calculated. This is a minimum figure since it has been assumed that all 27 children were correctly vaccinated and that all of the cases therefore represent vaccine failure.

In actuality some of these patients did not receive vaccine under ideal conditions. Eight of the 27 previously vaccinated patients had been vaccinated by nurses from the Texarkana/Bowie County Health Unit at a day nursery. The vaccine for these eight children had been carried back and forth to the nursery from the Health Unit in a cooler in a car on three separate days in June and July 1970. Although a lapse in technique which allowed warming of the vaccine cannot be documented here, it is a possible explanation.

An additional seven patients had been vaccinated under the age of 1 year. These children were vaccinated in the years 1963-67 when it was recommended that measles vaccine be given at age 9 months. It has since been learned that a vaccine failure rate as high as 15% may accompany vaccination at 9 months in the United States.

Question 15: What is the WHO recommended age for measles vaccination in developing countries? Why is the recommended age for vaccination different in the United States?

Answer 15
The WHO recommended age for measles vaccination is 9 months. This includes vaccination of all eligible children, even sick or malnourished. Despite the fact that up to 15% of the children may fail to respond at this age, the decision has to be balanced with the fact that some of these children would develop measles (and some would die) from the disease if immunization were delayed until 15 months. To cover those children who may not develop antibodies in response to the first dose of vaccine, WHO has recently added a recommendation that all children should have a second opportunity to receive measles vaccination.

In the United States (and many other developed countries), the recommended age for the first dose of measles vaccine is between 12 and 15 months and, for the second dose, between 4 and 6 years, i.e., before school entry. Because prevalence of measles is low and nutrition is high in these countries, the risk that a child between the ages of 9 and 15 months would contract measles is quite small, and the risk of death is even smaller.

PART V - CONCLUSION

Prior to the development of a vaccine, about 500,000 people developed measles in the United States annually; 50% of persons contracted the disease by age 6 years and 90% by age 15 years. In 1963 both a killed measles vaccine (KMV) and a live, attenuated vaccine were licensed. Since 1969 only live attenuated vaccine has been used in this country.

At the time of original licensure in 1963, the recommended age of vaccination in the United States was 9 months. The recommended age was raised to 12 months in 1965 and to 15 months in 1976.

Compared with the pre-vaccination era, the occurrence of measles in the U.S. declined by more than 99% by the late 1980s. However, measles cases increased in 1989-1991, and a two-dose strategy was adopted. After the adoption of the two-dose strategy and a substantial increase in immunization program resources, measles cases again declined. Since 1997, fewer than 140 cases of measles have been reported each year in the United Sates, almost all of which could be traced to imported cases. The provisional total for 2002 was a record low of 37 cases.

REFERENCES

1.   Landrigan PJ. Epidemic measles in a divided city. *JAMA* 1972; 221: 567-570.

2.   CDC. Case definitions for infectious conditions under public health surveillance. *MMWR* 1997;46(No. RR-10):23-24.

3.   WHO. Core information for the development of immunization policy: 2002 update. Geneva: World Health Organization, 2003.

ADDITIONAL READING

1.   Orenstein WA, Bernier RH, Hinman AR. Assessing vaccine efficacy in the field: further observations. *Epidemiologic Reviews* 1988; 10: 212-241.

2.   CDC. Measles, mumps, and rubella – vaccine use and strategies for elimination of measles, rubella and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1998; 47 (No. RR-8): 1-57.